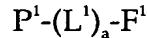


What is claimed is:

1. A composition of matter of the formula



and multimers thereof, wherein:

5 F¹ is a vehicle and is attached at the C-terminus of P¹-(L¹)_a;

P¹ is a PTH/PTHrP modulating domain;

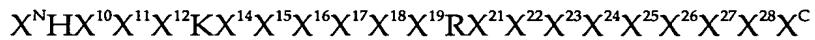
L^1 is a linker; and

a is 0 or 1.

2. The composition of matter of Claim 1 of the formulae



3. The composition of matter of Claim 1, wherein F¹ is an Fc domain.
4. The composition of matter of Claim 1 wherein F¹ is an IgG Fc domain.
5. The composition of matter of Claim 1 wherein F¹ is an IgG1 Fc domain.
6. The composition of matter of Claim 1 wherein F¹ comprises the sequence of SEQ ID NO: 2.
7. The composition of matter of Claim 1 wherein the PTH/PTHrP modulating domain is of the formula



(SEQ ID NO: 3)

wherein:

X^N is absent or is $X^3X^4X^5X^6X^7$, $X^2X^3X^4X^5X^6X^7$, $X^1X^2X^3X^4X^5X^6X^7$, or $YX^1X^2X^3X^4X^5X^6X^7$.

25 X^1 through X^7 , X^{10} , X^{11} , X^{12} , X^{14} through X^{28} are each
independently amino acid residues;

X^C is absent or is $X^{29}, X^{29}X^{30}, X^{29}X^{30}X^{31}, X^{29}X^{30}X^{31}X^{32}$.

is absent or is $X^{29}X^{30}X^{31}X^{32}$,
 $X^{29}X^{30}X^{31}X^{32}X^{33}$, $X^{29}X^{30}X^{31}X^{32}X^{33}X^{34}$, $X^{29}X^{30}X^{31}X^{32}X^{33}X^{34}X^{35}$, or
 $X^{29}X^{30}X^{31}X^{32}X^{33}X^{34}X^{35}X^{36}$;

X^{29} through X^{36} are each independently amino acid residues.

8. The composition of matter of Claim 7, wherein:

X^N is $X^1X^2X^3X^4X^5X^6X^7$;

X^1 is a hydrophilic or nonfunctional residue;

5 X^2 is V;

X^3 is S;

X^4 is E;

X^5 is a nonfunctional or basic residue;

10 X^6 is Q;

X^7 is L;

X^{10} is an acidic or hydrophilic residue;

X^{11} is a nonfunctional or basic residue;

X^{12} is a nonfunctional residue;

X^{14} is a basic or hydrophilic residue;

15 X^{15} is a nonfunctional residue;

X^{16} is a nonfunctional or hydrophilic residue;

X^{17} is an acidic, hydrophilic, or nonfunctional residue;

X^{18} is a nonfunctional residue;

X^{19} is an acidic or basic residue;

20 X^{21} is a nonfunctional or basic residue;

X^{22} is a hydrophilic, acidic, or aromatic residue;

X^{23} is an aromatic or lipophilic residue;

X^{24} is a lipophilic residue (L preferred);

~~X^{25} is a hydrophilic or basic residue;~~

25 X^{26} is a hydrophilic or basic residue;

X^{27} is a lipophilic, basic, or nonfunctional residue; and

X^{28} is a lipophilic or nonfunctional residue.

9. The composition of matter of Claim 8, wherein:

X^C is $X^{29}X^{30}X^{31}X^{32}X^{33}X^{34}$;

X^{29} is a hydrophilic or nonfunctional residue;
 X^{30} is a hydrophilic or acidic residue;
 X^{31} is a lipophilic or nonfunctional residue;
 X^{32} is H;
5 X^{33} is a hydrophilic residue; and
 X^{34} is a nonfunctional or aromatic residue.

10. The composition of matter of Claim 8, wherein:

X^C is $X^{29}X^{30}X^{31}$;
10 X^{29} is a hydrophilic or nonfunctional residue;
 X^{30} is a hydrophilic or acidic residue; and
 X^{31} is a lipophilic or nonfunctional residue.

11. The composition of matter of Claim 8, wherein:

X^C is $X^{29}X^{30}$;
15 X^{29} is a hydrophilic or nonfunctional residue; and
 X^{30} is a hydrophilic or acidic residue.

12. The composition of matter of Claim 8, wherein:

X^C is X^{29} ; and
 X^{29} is a hydrophilic or nonfunctional residue.

13. The composition of matter of Claim 8, wherein X^C is absent.

20 14. The composition of matter of Claim 8, wherein:

X^1 is A, S or Y;
 X^5 is H or I;
 X^{10} is N or D;
25 X^{11} is L, R, or K;
 X^{12} is G, F, or W;
 X^{14} is H or S;
 X^{15} is L or I;
 X^{16} is Q, N, S, or A;
 X^{17} is S, D, or L;

X^{18} is M, L, V or Nle;
 X^{19} is E or R;
 X^{21} is V, M, R, or Nle;
 X^{22} is E or F;
5 X^{23} is W or F;
 X^{25} is R or H;
 X^{26} is K or H;
 X^{27} is K or L; and
 X^{28} is L or I.

10 15. The composition of matter of Claim 14, wherein:

X^C is $X^{29}X^{30}X^{31}X^{32}X^{33}X^{34}$;
 X^{29} is Q or A;
 X^{30} is D or E;
 X^{31} is V or I;
15 X^{33} is N or T; and
 X^{34} is A, F or Y.

16. The composition of matter of Claim 14, wherein:

X^C is $X^{29}X^{30}X^{31}$;
 X^{29} is Q or A;
20 X^{30} is D or E; and
 X^{31} is V or I;

17. The composition of matter of Claim 14, wherein:

X^C is $X^{29}X^{30}$;
 X^{29} is Q or A; and
25 X^{30} is D or E.

18. The composition of matter of Claim 14, wherein:

X^C is X^{29} ; and
 X^{29} is Q or A.

19. The composition of matter of Claim 14, wherein X^C is absent.

20. The composition of matter of Claim 1, wherein the PTH/PTHrP modulating domain is of the formula

$J^N J^7 J^8 H N J^{11} J^{12} K H L J^{16} S J^{18} J^{19} R J^{21} E W L R K K L J^C$
(SEQ ID NO: 4)

5 wherein:

J^N is absent or is selected from $J^1 J^2 J^3 J^4 J^5 J^6$, $J^2 J^3 J^4 J^5 J^6$, $J^3 J^4 J^5 J^6$;
 J^1 is an amino acid residue;
 J^2 is an amino acid residue;
 J^3 is an amino acid residue;
10 J^4 is an amino acid residue;
 J^5 is an amino acid residue;
 J^6 is an amino acid residue;
 J^7 is an amino acid residue;
 J^8 is an amino acid residue;
15 J^{11} is a nonfunctional or basic residue;
 J^{12} is an amino acid residue;
 J^{16} is an amino acid residue;
 J^{18} is an amino acid residue;
 J^{19} is an acidic or basic residue;
20 J^{21} is an amino acid residue;
 J^C is absent or is J^{29} , $J^{29} J^{30}$, $J^{29} J^{30} J^{31}$, $J^{29} J^{30} J^{31} J^{32}$, $J^{29} J^{30} J^{31} J^{32} J^{33}$,
 $J^{29} J^{30} J^{31} J^{32} J^{33} J^{34}$; and
 J^{29} is an amino acid residue;
25 ~~J^{30} is an amino acid residue;~~
 J^{31} is an amino acid residue;
 J^{32} is an amino acid residue;
 J^{33} is an amino acid residue;
 J^{34} is an amino acid residue.

21. The composition of matter of Claim 20, wherein:

J^N is $J^1J^2J^3J^4J^5J^6$;

J^1 is a nonfunctional or aromatic residue;

J^2 is a nonfunctional residue;

J^3 is a hydrophilic residue;

5 J^4 is an acidic residue;

J^5 is a nonfunctional residue;

J^6 is a basic residue;

J^7 is a nonfunctional or aromatic residue;

J^8 is a nonfunctional residue;

10 J^{11} is a basic or a nonfunctional residue;

J^{12} is a nonfunctional or aromatic residue;

J^{16} is a nonfunctional or hydrophilic residue;

J^{18} is a nonfunctional residue;

J^{19} is an acidic or basic residue; and

15 J^{21} is a nonfunctional residue;

J^C is $J^{29}J^{30}J^{31}J^{32}J^{33}J^{34}$;

J^{29} is a hydrophilic or nonfunctional residue;

J^{30} is a hydrophilic or acidic residue;

J^{31} is a lipophilic or nonfunctional residue;

20 J^{32} is a basic residue;

J^{33} is an acidic residue; and

J^{34} is an aromatic residue.

22. The composition of matter of Claim 21, wherein:

25 J^1 is A, S or Y;

J^2 is V;

J^3 is S;

J^4 is E;

J^5 is I;

J^6 is Q;

J⁷ is L or F;
J⁸ is M or Nle;
J¹¹ is L, R, or K;
J¹² is G or W;
5 J¹⁶ is N, S, or A;
J¹⁸ is M, Nle, L, or V;
J¹⁹ is E or R;
J²¹ is V, M, or Nle;
J²⁹ is Q or A;
10 J³⁰ is D or E;
J³¹ is V or I;
J³² is H;
J³³ is N; and
J³⁴ is F or Y.

15 23. The composition of matter of Claim 20, wherein:

J^N is JJJ²J³J⁴J⁵J⁶;

J¹ is a nonfunctional or aromatic residue;

J² is a nonfunctional residue;

J³ is a hydrophilic residue;

20 J⁴ is an acidic residue;

J⁵ is a nonfunctional residue;

J⁶ is a basic residue;

J⁷ is a nonfunctional or aromatic residue;

J⁸ is a nonfunctional residue;

25 J¹¹ is a basic or a nonfunctional residue;

J¹² is a nonfunctional or aromatic residue;

J¹⁶ is a nonfunctional or hydrophilic residue;

J¹⁸ is a nonfunctional residue;

J¹⁹ is an acidic or basic residue;

J^{21} is a nonfunctional residue;
 J^C is $J^{29}J^{30}J^{31}$;
 J^{29} is a hydrophilic or nonfunctional residue;
 J^{30} is a hydrophilic or acidic residue; and
5 J^{31} is a lipophilic or nonfunctional residue.

24. The composition of matter of Claim 23, wherein:

10 J^1 is A, S or Y;
 J^2 is V;
 J^3 is S;
 J^4 is E;
 J^5 is I;
 J^6 is Q;
 J^7 is L or F;
 J^8 is M or Nle;
15 J^{11} is L, R, or K;
 J^{12} is G or W;
 J^{16} is N, S, or A;
 J^{18} is M, Nle, L, or V;
 J^{19} is E or R;
20 J^{21} is V, M, or Nle;
 J^{29} is Q or A;
 J^{30} is D or E; and
 J^{31} is V or I.

25. The composition of matter of Claim 20, wherein:

25 J^N is $J^1J^2J^3J^4J^5J^6$;
 J^1 is a nonfunctional or aromatic residue;
 J^2 is a nonfunctional residue;
 J^3 is a hydrophilic residue;
 J^4 is an acidic residue;

J⁵ is a nonfunctional residue;
J⁶ is a basic residue;
J⁷ is a nonfunctional or aromatic residue;
J⁸ is a nonfunctional residue;
5 J¹¹ is a basic or a nonfunctional residue;
J¹² is a nonfunctional or aromatic residue;
J¹⁶ is a nonfunctional or hydrophilic residue;
J¹⁸ is a nonfunctional residue;
10 J¹⁹ is an acidic or basic residue;
J²¹ is a nonfunctional residue;
J^C is J²⁹J³⁰;
J²⁹ is a hydrophilic or nonfunctional residue; and
J³⁰ is a hydrophilic or acidic residue.

26. The composition of matter of Claim 25, wherein:

15 J¹ is A, S or Y;
J² is V;
J³ is S;
J⁴ is E;
J⁵ is I;
20 J⁶ is Q;
J⁷ is L or F;
J⁸ is M or Nle;
J¹¹ is L, R, or K;
J¹² is G or W;

25 J¹⁶ is N, S, or A;
J¹⁸ is M, Nle, L, or V;
J¹⁹ is E or R;
J²¹ is V, M, or Nle;
J²⁹ is Q or A; and

J^{30} is D or E.

27. The composition of matter of Claim 20, wherein:

J^N is $J^1J^2J^3J^4J^5J^6$;

J^1 is a nonfunctional or aromatic residue;

5 J^2 is a nonfunctional residue;

J^3 is a hydrophilic residue;

J^4 is an acidic residue;

J^5 is a nonfunctional residue;

J^6 is a basic residue;

10 J^7 is a nonfunctional or aromatic residue;

J^8 is a nonfunctional residue;

J^{11} is a basic or a nonfunctional residue;

J^{12} is a nonfunctional or aromatic residue;

J^{16} is a nonfunctional or hydrophilic residue;

15 J^{18} is a nonfunctional residue;

J^{19} is an acidic or basic residue;

J^{21} is a nonfunctional residue;

J^C is J^{29} ; and

J^{29} is a hydrophilic or nonfunctional residue.

20 28. The composition of matter of Claim 27, wherein:

J^1 is A, S or Y;

J^2 is V;

J^3 is S;

J^4 is E;

25 J^5 is I;

J^6 is Q;

J^7 is L or F;

J^8 is M or Nle;

J^{11} is L, R, or K;

J¹² is G or W;
J¹⁶ is N, S, or A;
J¹⁸ is M, Nle, L, or V;
J¹⁹ is E or R;
5 J²¹ is V, M, or Nle; and
J²⁹ is Q or A.

29. The composition of matter of Claim 20, wherein:

J^N is J¹J²J³J⁴J⁵J⁶;
10 J¹ is a nonfunctional or aromatic residue;
J² is a nonfunctional residue;
J³ is a hydrophilic residue;
J⁴ is an acidic residue;
J⁵ is a nonfunctional residue;
J⁶ is a basic residue;
15 J⁷ is a nonfunctional or aromatic residue;
J⁸ is a nonfunctional residue;
J¹¹ is a basic or a nonfunctional residue;
J¹² is a nonfunctional or aromatic residue;
J¹⁶ is a nonfunctional or hydrophilic residue;
20 J¹⁸ is a nonfunctional residue;
J¹⁹ is an acidic or basic residue;
J²¹ is a nonfunctional residue; and
J^C is absent.

30. The composition of matter of Claim 29, wherein:

25 J¹ is A, S or Y;
J² is V;
J³ is S;
J⁴ is E;
J⁵ is I;

J⁶ is Q;
 J⁷ is L or F;
 J⁸ is M or Nle;
 J¹¹ is L, R, or K;
 5 J¹² is G or W;
 J¹⁶ is N, S, or A;
 J¹⁸ is M, Nle, L, or V;
 J¹⁹ is E or R; and
 J²¹ is V, M, or Nle.

10 31. The composition of matter of Claim 20, wherein the PTH/PTHrP modulating domain is selected from Table 1.

32. The composition of matter of Claim 1 wherein the PTH/PTHrP modulating domain is of the formula

O^NLHO¹⁰O¹¹O¹²KSIO¹⁶O¹⁷LRRRFO²³LHHLIO^C
 15 (SEQ ID NO: 5)

wherein:

O^N is absent or is YO¹O²O³O⁴O⁵O⁶O⁷, O¹O²O³O⁴O⁵O⁶O⁷,
 O²O³O⁴O⁵O⁶O⁷, O³O⁴O⁵O⁶O⁷, O⁴O⁵O⁶O⁷, O⁵O⁶O⁷, O⁶O⁷, or
 O⁷;

20 O¹ is an amino acid residue;
 O² is an amino acid residue;
 O³ is an amino acid residue;
 O⁴ is an amino acid residue;
 O⁵ is an amino acid residue;

25 O⁶ is an amino acid residue;
 O⁷ is an amino acid residue;
 O¹⁰ is an amino acid residue;
 O¹¹ is an amino acid residue;
 O¹² is an amino acid residue;

5 O¹⁶ is an amino acid residue;
 O¹⁷ is an amino acid residue;
 O²³ is an amino acid residue;
 O^C is absent or is O²⁹, O²⁹O³⁰, O²⁹O³⁰O³¹, O²⁹O³⁰O³¹O³²,
 O²⁹O³⁰O³¹O³²O³³, O²⁹O³⁰O³¹O³²O³³O³⁴, O²⁹O³⁰O³¹O³²O³³O³⁴O³⁵,
 or O²⁹O³⁰O³¹O³²O³³O³⁴O³⁵O³⁶; and
 O²⁹ through O³⁶ are each independently amino acid residues.

33. The composition of matter of Claim 27, wherein:

10 O^N is O^7 ;
 O^7 is a nonfunctional residue;
 O^{10} is an acidic or hydrophilic residue;
 O^{11} is a basic or nonfunctional residue;
 O^{12} is an aromatic or nonfunctional residue;
 O^{15} is a hydrophilic or nonfunctional residue;
15 O^{16} is a hydrophilic residue;
 O^{17} is an acidic or nonfunctional residue;
 O^{23} is an aromatic residue; and
 O^C is absent.

34. The composition of matter of Claim 23, wherein:

20 O^N is $O^1O^2O^3O^4O^5O^6O^7$;
 O^1 is a nonfunctional amino acid residue;
 O^2 is a nonfunctional amino acid residue;
 O^3 is a hydrophilic amino acid residue;
 O^4 is an acidic amino acid residue;
 O^5 is a basic or nonfunctional amino acid residue;
 O^6 is a hydrophilic amino acid residue;
 O^7 is a nonfunctional residue;
 O^{10} is an acidic or hydrophilic residue;
 O^{11} is a basic or nonfunctional residue;

- O¹² is an aromatic or nonfunctional residue;
- O¹⁵ is a hydrophilic or nonfunctional residue;
- O¹⁶ is a hydrophilic residue; and
- O¹⁷ is an acidic or nonfunctional residue; and
- O²³ is an aromatic residue.

35. The composition of matter of Claim 34, wherein:

O^1 is A ;

O² is V;

O³ is S;

10 O^4 is E;

O⁵ is H or I;

O⁶ is Q;

O⁷ is L;

O¹⁰ is N

O^{12} is G, F, or

O¹⁵ is I or S;

O¹⁶ is Q or N;

O¹⁷ is D or L

20 O^{23} is F or W.

36. The composition of

36. The composition of matter of Claim 27, wherein the PTH/PTHrP modulating domain is selected from Table 2.

37. The composition of matter of Claim 1, wherein the PTH/PTHrP modulating domain has the amino acid sequence of TIP39.

25 38. The composition of matter of Claim 1, comprising a sequence
selected from Table 4.

39. A composition of matter, which comprises a peptide selected from SEQ ID NOS: 17, 18, 19, and 69.

40. A nucleic acid encoding a composition of matter of Claim 1.

41. A nucleic acid encoding a composition of matter of Claim 7.

42. A nucleic acid encoding a composition of matter of Claim 20.

43. A nucleic acid encoding a composition of matter of Claim 32.

44. A nucleic acid encoding a composition of matter of Claim 39.

5 45. An expression vector comprising the DNA of Claim 40.

46. An expression vector comprising the DNA of Claim 41.

47. An expression vector comprising the DNA of Claim 42.

48. An expression vector comprising the DNA of Claim 43.

49. An expression vector comprising the DNA of Claim 44.

10 50. A host cell comprising the expression vector of Claim 45.

51. A host cell comprising the expression vector of Claim 46.

52. A host cell comprising the expression vector of Claim 47.

53. A host cell comprising the expression vector of Claim 48.

54. A host cell comprising the expression vector of Claim 49.

15 55. The cell of Claim 50, wherein the cell is an E. coli cell.

56. The cell of Claim 51, wherein the cell is an E. coli cell.

57. The cell of Claim 52, wherein the cell is an E. coli cell.

58. The cell of Claim 53, wherein the cell is an E. coli cell.

59. A process for preparing an antagonist of the PTH/PTHrP receptor,

20 which comprises:

a) selecting at least one peptide that binds to the receptor; and

b) preparing a pharmacologic agent comprising at least one Fc domain covalently linked to at least one amino acid sequence of the selected peptide or peptides.

25 60. The process of Claim 59, wherein the peptide is selected from the SEQ ID NOS: 3, 4, or 5.

61. The process of Claim 59, wherein the peptide is selected in a process comprising screening of a phage display library, an E. coli

display library, a ribosomal library, an RNA-peptide library, or a chemical peptide library.

62. The process of Claim 59, wherein the preparation of the pharmacologic agent is carried out by:

5 a) preparing a gene construct comprising a nucleic acid sequence encoding the selected peptide and a nucleic acid sequence encoding an Fc domain; and

 b) expressing the gene construct.

63. The process of Claim 59, wherein the gene construct is expressed in an E. coli cell.

10 64. The process of Claim 59, wherein the selection of the peptide is carried out by a process comprising:

15 a) preparing a gene construct comprising a nucleic acid sequence encoding a first selected peptide and a nucleic acid sequence encoding an Fc domain;

 b) conducting a polymerase chain reaction using the gene construct and mutagenic primers, wherein

20 i) a first mutagenic primer comprises a nucleic acid sequence complementary to a sequence at or near the 5' end of a coding strand of the gene construct, and

 ii) a second mutagenic primer comprises a nucleic acid sequence complementary to the 3' end of the noncoding strand of the gene construct.

65. A method of treating osteopenia, which comprises administering a PTH agonist and a bone resorption inhibitor, wherein the PTH agonist comprises a composition of matter of Claim 1.

25 66. A method of treating osteopenia, which comprises administering a PTH agonist and a bone resorption inhibitor, wherein the PTH agonist comprises a composition of matter of Claim 7.

67. A method of treating osteopenia, which comprises administering a PTH agonist and a bone resorption inhibitor, wherein the PTH agonist comprises a composition of matter of Claim 20.

68. A method of treating osteopenia, which comprises administering a PTH agonist and a bone resorption inhibitor, wherein the PTH agonist comprises a composition of matter of Claim 32.

5 69. A method of treating osteopenia, which comprises administering a PTH agonist and a bone resorption inhibitor, wherein the PTH agonist comprises a composition of matter of Claim 39.

10 70. The method of Claim 65, wherein the bone resorption inhibitor is selected from OPG, OPG-L antibody, calcitonin, bisphosphonates, estrogens, estrogen receptor modulators, and tibolone.

71. The method of Claim 66, wherein the bone resorption inhibitor is selected from OPG, OPG-L antibody, calcitonin, bisphosphonates, estrogens, estrogen receptor modulators, and tibolone.

15 72. The method of Claim 67, wherein the bone resorption inhibitor is selected from OPG, OPG-L antibody, calcitonin, bisphosphonates, estrogens, estrogen receptor modulators, and tibolone.

73. The method of Claim 68, wherein the bone resorption inhibitor is selected from OPG, OPG-L antibody, calcitonin, bisphosphonates, estrogens, estrogen receptor modulators, and tibolone.

20 74. The method of Claim 69, wherein the bone resorption inhibitor is selected from OPG, OPG-L antibody, calcitonin, bisphosphonates, estrogens, estrogen receptor modulators, and tibolone.

25 75. A method of treating osteopenia, which comprises administering a composition of matter of Claim 1.

76. A method of treating osteopenia, which comprises administering a composition of matter of Claim 7.

77. A method of treating osteopenia, which comprises administering a composition of matter of Claim 20.
78. A method of treating osteopenia, which comprises administering a composition of matter of Claim 32.
- 5 79. A method of treating osteopenia, which comprises administering a composition of matter of Claim 39.